REMARKS

Claims 98-104 and 117-134 are pending in the subject application. By this Amendment, applicants have canceled claim 117 and amended claims 98, 100-102, and 118-134 to more clearly define their invention. Certain amendments are made to more clearly indicate that the "fragment" recited in the claims refers to a fragment of an antibody and not to a fragment of a hybridoma cell line. Applicants maintain that these amendments do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 98-104, and 118-134, as amended, will be pending and under examination.

Applicants thank the Examiner for the courtesy extended during a telephone interview with the undersigned on September 8, 2005. An Interview Summary for this telephone interview was issued September 13, 2005. Applicants' arguments made during the September 8, 2008 telephone interview are repeated and elaborated upon below. Additional support for applicants' arguments may be found in three publications attached hereto.

The Invention

The invention claimed in the subject application is a monoclonal antibody designated PA14 produced by a hybridoma cell line designated PA14 (ATCC Accession No. HB-12610) or a fragment of antibody PA14 which binds to a single epitope of chemokine receptor 5 (CCR5) present on the surface of a cell expressing CCR5. This epitope comprises a combination of amino acid residues in (a) the N-terminus of CCR5, and (b) the

second extracellular loop of CCR5. The invention also provides a monoclonal antibody or a fragment of such antibody which binds to the same epitope as monoclonal antibody PA14.

Rejections under 35 U.S.C. §112

35 U.S.C. §112, Second Paragraph

In the July 11, 2005 Final Office Action, the Examiner rejected claims 98, 102-104 and 129-134 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner stated that amended claim 98 recites "the hybridoma cell line ... or a fragment thereof ...". The Examiner also stated that while it is presumed that applicants intend to claim fragments of the antibody PA14 and not fragments of the cell line, this intention is not evident from the claim language. The Examiner additionally stated that this rejection also affects claims 102-104.

In response, without conceding the correctness of the Examiner's position, applicants note that claims 98 and 100-102, as amended, clearly indicate that "fragment" refers to a fragment of an antibody, not a fragment of a hybridoma cell line. Claims 103, 104, and 129-134 depend, directly or indirectly, from one of claims 100, 101 or 102 and therefore necessarily possess all the elements of claims 100, 101 or 102. Accordingly, applicants maintain that claims 98, 102-104, and 129-134, as amended, satisfy the requirements of 35 U.S.C. §112, second paragraph. Applicants respectfully request, therefore, that the Examiner withdraw this ground of

objection.

The Examiner also stated that claims 129-134 are drawn to a monovalent antibody. The Examiner noted that these claims ultimately depend from amended claims 100 and 101, which require that the antibody (or fragment of such antibody) bind to the same epitope as monoclonal antibody (mAb) PA14 or have the CDRs derived from the PA14 hybridoma. The Examiner contended that PA14 has bispecificity to a combination of two epitope valencies comprising an amino acid at the N-terminus (Nt) and an amino acid within the second extracellular loop (ECL2), and therefore the monovalent antibody of claims 129-134 contradicts the required elements of claims 100 and 101 since such monovalent antibody would only be specific for one valency.

In response, applicants respectfully traverse this rejection. Applicants disagree, in particular, with the Examiner's assertion that "PA14 has bi-specificity to a combination of two epitope valencies". Applicants assert that, on the contrary, PA14 is clearly monospecific, i.e., it binds to a single epitope of the CCR5 receptor. In support of this assertion, applicants note that PA14 is an IgG monoclonal antibody produced by immunizing female Balb/c mice with L1.2-CCR5^{+} cells, and fusing the splenocytes with the Sp2/0 myeloma cell line. See the specification at page 26, lines 12-22; see also page 26, 22-36; and page 31, lines 5-6. Applicants respectfully point out that an IgG1 antibody, such as mAb PA14, is necessarily monospecific and bivalent. See, e.g., paragraphs 0002-0004 of Zhu (2002) U.S. Publication No. 2002/0103345 A1; henceforth "Zhu" (the cover page, pages 1-2, and Fig. 1 of which are attached hereto as **Exhibit A**).

Applicants are unclear what the Examiner means by "a combination of two epitope valencies". Valency refers to the number of binding sites which an antigen-binding protein has for a particular epitope. See Zhu, paragraph 0004. Thus, to characterize the PA14 antibody as bivalent simply means that it has two identical epitope binding sites. In other words, the monospecific, bivalent mAb PA14 has two identical epitope binding sites, each of which recognizes an identical epitope.

Applicants note that the single epitope to which PA14 mAb binds comprises a combination of amino acid residues in (a) the Nt of CCR5, and (b) the ECL2 of CCR5. The Examiner appears to misinterpret this fact to mean that mAb PA14 binds to two epitopes, one epitope in the Nt, and a second epitope in the ECL2 of CCR5. Applicants respectfully assert that this interpretation is incorrect. In this regard, applicants emphasize that the participation of amino acid residues from linearly noncontiguous regions of CCR5, i.e., the Nt and ECL2 regions, in forming the single epitope to which mAb PA14 binds, does not mean that PA14 binds to two different epitopes, one in the Nt region and the other in the ECL2 regions. Applicants point out that the three-dimensional folding of the CCR5 receptor on the surface of a cell brings certain amino acid residues in the Nt in sufficient proximity to certain residues in the ECL2 to form a conformational epitope which does not exist in the linear CCR5 protein molecule. The particular conformational epitope recognized by mAb PA14, which is a single epitope, includes D2 in the Nt, and R168 and Y176 in the ECL2. See the specification at page 32, lines 16-18. Applicants note that the specification discloses experimental data indicating that PA14 does not bind

to reduced and denatured CCR5 protein. See the specification at page 32, lines 15-18. This confirms that mAb PA14 recognizes a conformational epitope resulting from the three-dimensional structure of the CCR5 receptor when the receptor is expressed on the surface of a cell.

Applicants also maintain, for the reasons set forth herein, that there is no inconsistency between the subject matter of claims 129-134 and that of claims 100 and 101.

First, ta mAb (or fragment of such mAb) which binds to the same epitope as mAb PA14 (as claimed in claim 100), or which has the CDRs derived from the PA14 hybridoma (as claimed in claim 101), necessarily has an epitope binding site that binds to the single epitope recognized by antibody PA14. If such mAb is, for example, an IgG antibody (though it need not be limited to this type of antibody), it will have two epitope binding sites that independently bind to the single epitope recognized by mAb PA14, i.e., it will be a monospecific, bivalent mAb.

Second, one group of antibody fragments, among the many conceivable fragments of the antibody claimed in claims 100 and 101, comprises monovalent antibody fragments, i.e., antibody fragments containing a single epitope binding site which binds to the single epitope recognized by mAb PA14. Examples of such monovalent antibody fragments include Fab, Fv and scFv fragments (see Zhu, paragraph 0005 and Figure 1; **Exhibit A**). Accordingly, applicants maintain that there is no inconsistency between claims 129-134 and claims 100 and 101 from which they depend. Applicants therefore respectfully request that the Examiner reconsider and withdraw this ground

of rejection.

35 U.S.C. §112, First Paragraph

The Examiner rejected claims 98 and 102-104 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner also stated that, as discussed above, claim 98 encompasses fragments of the hybridoma cell line, PA14. The Examiner further stated that there is no support for this concept in the original disclosure and the recitation thereof presents new matter. The Examiner requested that applicants either cancel the new matter or point to support for this concept.

In response, without conceding the correctness of the Examiner's position, applicants reiterate that claims 98 and 102, as amended, clearly indicate that the "fragment" is a fragment of an antibody, not a fragment of a hybridoma cell line. Applicants note that claims 103 and 104 depend, directly or indirectly, from claim 102 and therefore possess all the elements of claim 102. Thus, claims 98 and 102-104, as amended, do not encompass fragments of a hybridoma cell line. Accordingly, applicants maintain that claims 98 and 102-104, as amended, satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw this ground of rejection.

Double Patenting

The Examiner provisionally rejected claims 98-104 and 117-122 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 99-105 of copending U.S. Application No. 10/763,545 ("the '545 application) which corresponds to U.S. Publication No. 2004/0228869. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a mAb, PA14, or a fragment thereof, produced from a hybridoma cell line, PA14, that binds to the Nt of CCR5 and the ECL2 of CCR5.

The Examiner also provisionally rejected claims 124, 127, 128, 130, 133 and 134 for obviousness-type double patenting as allegedly unpatentable over claims 99-105 of the '545 application in view of Wu et al. (WO 98/18826; henceforth "Wu"). The Examiner asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make mAbs of the '545 application for monovalent specificity to one particular epitope in the region of interest, with a reasonable expectation of success for making such antibodies because Wu teaches mAbs that recognize the same or similar epitopes as those recognized by mAbs disclosed in the '545 application.

In response, applicants respectfully traverse the above provisional obviousness-type double patenting rejections. Applicants disagree, in particular, with the Examiner's assertion that Wu teaches mAbs that recognize the same or similar epitopes as those recognized by mAbs disclosed in the

'545 application. This issue is discussed in more detail below in response to the rejections under 35 U.S.C. §102(a) and §103(a). However, for the purposes of the instant provisional obviousness-type double patenting rejections, and without conceding the correctness of the Examiner's position, applicants note that this is a "provisional" rejection over the '545 application which is not an allowed application. Accordingly, if the claims of the subject application are otherwise allowable, the "provisional" double patenting rejection should be withdrawn and the claims in the subject application should be allowed and issued, whereby the claims of the '545 application would become subject to an obviousness-type double patenting rejection.

Rejections under 35 U.S.C. §102(a)

The Examiner rejected claims 100, 102, 103, 117, 123 and 129 under 35 U.S.C. §102(a) as allegedly anticipated by Wu et al. (WO 98/18826) ("Wu"). The Examiner stated that applicants argue that the instant antibodies are distinct from the antibodies of Wu because the claimed PA14 antibody binds to both the Nt and the ECL2 of CCR5 and the antibodies of Wu bind to one or the other.

The Examiner noted that she has reviewed the Wu reference in view of applicants' arguments. The Examiner also stated that, contrary to applicants' assertions, Wu specifically anticipates bispecific antibodies that simultaneously bind to Nt and ECL2 of CCR5 (citing page 15, line 27 to page 16, line 5). The Examiner asserted that the bispecific antibody of Wu anticipates an antibody or a functional portion thereof "which has the same or similar epitopic specificity as at least two

of the antibodies described herein" (quoting from page 15, lines 28-30 of Wu). The Examiner further noted that Wu states that the bispecific antibody binds to the Nt and ECL2 and has the same or similar epitopic specificity as that of mAbs 2D7 and 5C7 (citing page 15, line 33 to page 16, line 5). The Examiner maintained that since the bispecific antibodies of Wu anticipate the same or similar epitopes recognized by 5C7 and 2D7, Wu anticipate a bispecific antibody or a fragment thereof that binds to the same epitopes as mAb PA14. The Examiner further asserted that the claimed PA14 mAb is equivalent to the bispecific antibodies encompassed by Wu as each has bispecificity (i.e., is bispecific) to a combination of two distinct epitopes comprising an amino acid at the Nt and an amino acid within ECL2.

In response, applicants note, first, that Wu discloses two types of antibodies: (1) murine mAbs such as 5C7, 3A9 and 2D7, produced by conventional hybridoma technology (see Wu, page 14, line 29 to page 15, line 2; page 65, line 8 to page 66, line 5; page 66, line 27 to page 67, line 5; page 72, lines 24-31); and (2) engineered bispecific antibodies which combine in a single antibody the epitopic specificity of at least two of the disclosed murine mAbs (see page 15, line 27 to page 16, line 5).

Applicants note that the murine mAbs disclosed in Wu are all IgG antibodies. See Wu, page 72, lines 30-31; see also Wu et al. (1997) J. Ex. Med. 185: 1681-1691 (listed as Reference 6 in the September 3, 2003 Information Disclosure Statement), page 1683, left col. Applicants assert that the murine IgG mAbs disclosed in Wu are necessarily monospecific, bivalent antibodies. That is, each mAb has two identical epitope

binding sites, each specific for the same single epitope. See paragraphs 0002-0004 of Zhu (**Exhibit A**).

Applicants note that Wu teaches that each of the murine mAbs disclosed therein binds to an epitope which is located in either the Nt or the ECL2 of CCR5, but not both. See page 15, lines 13-26; page 76, line 30 to page 77, line 23. Thus, for example, page 15, lines 18-21 of Wu disclose that mAbs 5C7 and 3A9 have "epitopic specificity for the amino-terminus of the CCR5 receptor. mAb 2D7 has epitopic specificity for the second extracellular loop of the CCR5 receptor."

Applicants direct the Examiner's attention to the following two publications which provide more detailed epitope mapping data for certain of the mAbs disclosed in Wu: C. Königs et al. (2000) Eur. J. Immunol. 30: 1162-1171 (henceforth "Königs"), and B. Lee et al. (1999) J. Biol. Chem. 274: 9617-9626 (henceforth "Lee"). Copies of these publications are attached hereto as References 1 and 2, respectively, in the Information Disclosure Statement included with this Amendment.

Königs defines the epitope for mAb 3A9 as comprising amino acid residues S6 or S7, I9, Y10 and D11 in the Nt, and F96 and G97 in the first extracellular loop (ECL1). See page 1166, left col. Königs also defines the epitope for mAb 5C7 as comprising amino acid residues P8 in the Nt, H88 and W94 in the ECL1, and possibly R274, L275, D276 in the third extracellular loop (ECL3). See page 1166, right col.

Lee used alanine scan mutagenesis to map the epitope specificities of eighteen anti-CCR5 mAbs, including 2D7 which is disclosed in Wu. Lee defines the epitope for mAb 2D7 as

comprising amino acid residues K171 and E172 in the ECL2. See page 9620, left col., first paragraph; page 9621, Figure 2B; and page 9625, paragraph spanning cols. Applicants note that these data are consistent with the disclosure in the subject application that the 2D7 epitope comprises Q170, K171 and E172 in the ECL2. See the specification at page 33, lines 18-19. As discussed in more detail below, applicants maintain that the epitope mapping data in Königs and Lee support applicants' position that the mAbs disclosed in Wu do not bind to an epitope to which mAb PA14 binds.

Applicants note that the other antibodies disclosed in Wu are bispecific antibodies which have been engineered to combine the epitopic specificity of at least two of the disclosed murine mAbs. Applicants note that bispecific antibodies necessarily contain two different epitope binding sites. See Zhu, paragraph 0003 (**Exhibit A**). Applicants note that IgG mAbs, such as PA14, 5C7 and 2D7, are necessarily monospecific, whereas bispecific antibodies such as those disclosed in Wu (see page 15, line 27 to page 16, line 5) have been engineered to contain two different epitope binding sites. See Zhu, paragraphs 0010-0013 (**Exhibit A**).

As Wu discloses, "a bispecific antibody of the present invention can have the same or similar epitopic specificity as [a combination of] mAb 2D7 and 5C7, e.g., binds the second extracellular loop, or portion thereof, and the amino terminal region, or portion thereof, of mammalian CCR5 protein." See page 15, line 33 to page 16, line 5). Bispecificity in the antibody is achieved by combining a portion of the monospecific 2D7 mAb containing a first epitope binding site (which binds to an epitope located exclusively within the

ECL2) with a portion of the monospecific 5C7 mAb containing a second epitope binding site (which, according to Wu binds to the Nt, and which, according to Königs, also binds to the ECL1, and possibly to the ECL3). The resulting bispecific antibody binds to two distinct epitopes, one epitope recognized by 2D7 and the other recognized by 5C7. Applicants note that the bispecific antibody having such epitope specificity forms the basis of the Examiner's anticipation rejection (see, e.g., the Final Office Action at page 7, first paragraph). Accordingly, this bispecific antibody is the one referred to below as "the bispecific antibody of Wu".

Contrary to the Examiner's characterization of applicants' argument, applicants do not assert that the claimed antibodies are distinct from the antibodies of Wu because the PA14 antibody binds to both the Nt and the ECL2 of CCR5, whereas the antibodies of Wu bind to one or the other. Although this distinction is applicable to the monospecific, murine mAbs disclosed in Wu and the disclosure therein of their epitopic specificity, applicants maintain that PA14, being a monospecific IgG mAb, binds to a single epitope which includes amino acid residues in both the Nt and the ECL2 of CCR5. See the specification at, *inter alia*, page 33, lines 17-18; page 38, lines 6-9; page 41, lies 21-22. In contrast, the engineered bispecific antibody of Wu binds to two distinct epitopes, one epitope comprising amino acid residues in the ECL2, and a second epitope comprising amino acid residues in the Nt (and also in the ECL1, and possibly in the ECL3, according to Königs).

There is no disclosure in Wu of an antibody that binds to a single epitope comprising amino acid residues in both the Nt

and the ECL2 of CCR5, let alone a disclosure of an antibody that binds to the epitope to which mAb PA14 binds. Since a finding of anticipation requires that a prior art reference teach each and every element of the rejected claims, and Wu does not disclose an antibody which binds to the single CCR5 epitope to which mAb PA14 binds, applicants maintain that the instant claims are not anticipated by Wu.

Applicants further refer to the Examiner's statement on page 6 of the Final Office Action that Wu specifically anticipates bispecific antibodies that simultaneously bind to the Nt and ECL2 of CCR5. In other words, Wu anticipates bispecific antibodies that simultaneously bind to two distinct epitopes, one in the Nt and the other in the ECL2 (as clearly indicated by Wu, page 15, line 27 to page 16, line 5). Thus parsed, it is clear that the Examiner's statement has no bearing on any of the antibodies claimed in the subject application since none of these claimed antibodies simultaneously binds to two distinct epitopes in the Nt and ECL2, respectively, of CCR5. In this regard, applicants respectfully submit that the Examiner is mistaken in asserting on page 7 of the Final Office Action that the claimed PA14 mAb is equivalent to the bispecific antibodies encompassed by Wu as "each has bi-specificity (i.e., bispecific) to a combination of two distinct epitopes comprising an amino acid at the Nt and an amino acid within ECL2" (emphasis added). In response, applicants reiterate that mAb PA14 is a monospecific antibody which binds to a single conformational epitope comprising amino acids in both the Nt and ECL2 of CCR5.

In conclusion, the CCR5 epitope recognized by mAb PA14 is not the epitope recognized by mAbs 2D7, 5C7 or any of the other

mAbs disclosed in Wu. The bispecific antibodies disclosed in Wu merely combine the specificities of two of the mAbs disclosed therein into a single antibody (see Wu, page 15, lines 27-30) but do not possess any novel epitopic specificity with regard to any single epitope. Thus, the CCR5 epitope recognized by mAb PA14 is not the same as, nor similar to either of the two distinct epitopes recognized by the bispecific antibodies disclosed in Wu. Since Wu does not disclose any antibody, either murine mAb or engineered bispecific antibody, which binds to the epitope to which mAb PA14 binds, the instant claims are not anticipated by Wu.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 104, 119, 120, 125, 126, 131 and 132 under 35 U.S.C. §103(a) as allegedly unpatentable over Wu (WO 98/18826) for reasons of record. The Examiner reiterated that the bispecific antibodies of Wu bind to the same epitopes as instantly claimed antibody PA14. Further, the Examiner maintained that it would have been obvious for one of ordinary skill in the art at the time the invention was made to obtain the antibody framework from any of the human immunoglobulins to maintain the conformation of the CDR region and to render the recombinant antibodies less immunogenic once administered. The Examiner also asserted that one of ordinary skill in the art would have been motivated to maintain the donor amino acid sequences immediately adjacent to the CDR domains to assure that when the framework portion of the antibody is added, the CDR domain remains intact. The Examiner further asserted that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because humanizing antibodies using human

IgG is conventional technique for humanizing recombinant antibodies. The Examiner concluded that the invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In response, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness of claims 104, 119, 120, 125, 126, 131 and 132. Applicants note that in accordance with M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

Applicants maintain that the Examiner has failed to satisfy any of the three requirements for establishing a *prima facie* case of obviousness. As applicants have discussed in detail above in response to the rejections under 35 U.S.C. §102(a), none of the antibodies disclosed in Wu, neither the murine monospecific mAbs nor the bispecific antibodies, binds to the epitope to which mAb PA14 binds. Applicants have also noted above that PA14 is a <u>monospecific</u>, bivalent mAb, having two identical epitope binding sites that independently bind to the same <u>single epitope</u> comprising amino acid residues D2 in the Nt, and R168 and Y176 in the ECL2 of CCR5. In contrast, the antibodies disclosed in Wu are (1) murine, <u>monospecific mAbs</u> such as 5C7, 3A9 and 2D7 which bind to a <u>single epitope</u> that

is not the same as the epitope recognized by PA14; or (2) engineered, bispecific antibodies which bind to two distinct epitopes corresponding to epitopes recognized by two of the murine, monospecific mAbs disclosed in Wu, neither of which is the conformational epitope to which mAb PA14 binds.

Further, applicants maintain that Wu does not provide any suggestion or motivation to make PA14 or a mAb with the same epitope specificity as PA14, nor does Wu provide any expectation of success in making such an antibody.

Accordingly, applicants maintain that the Examiner fails to satisfy the requirements for establishing a *prima facie* case of obviousness. Applicants therefore respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary of Arguments

Applicants respectfully submit that the rejections under 35 U.S.C. §102(a) and 103(a) set forth in the July 11, 2005 Final Office Action are predicated on the Examiner's incorrect interpretation that mAb PA14, or an antibody which binds to the same epitope as PA14, is a bispecific antibody which bind to two distinct epitopes, one located in the Nt region and the other located in the ECL2 region of CCR5.

To correct this error in interpretation, applicants have directed the Examiner's attention to a published reference (Zhu; see **Exhibit A**) that makes clear that IgG mAbs, such as PA14 and the murine mAbs disclosed in Wu, are invariably monospecific, bivalent antibodies which have two identical

epitope binding sites, each of which binds to an identical, single epitope. The specification discloses epitope mapping data demonstrating that PA14 binds to a single conformational epitope, say "X", which comprises D2 in the Nt, and R168 and Y176 in the ECL2, of CCR5. Wu discloses that mAb 5C7 binds specifically to an epitope, say "Y", comprising amino acids in the Nt. Subsequent data from Königs indicate that "Y" also comprises P8 in the Nt, H88 and W94 in the ECL1, and possibly R274, L275, D276 in the ECL3. Wu further teaches that mAb 2D7 binds specifically to an epitope, say "Z", in the ECL2. The specification of the subject application corroborates Wu's disclosure that 2D7 binds to an epitope located exclusively in the ECL2, and further discloses that that this epitope, "Z", comprises Q170, K171 and E172 in the ECL2. Consistent with these data, Lee discloses that "Z" comprises K171 and E172 in the ECL2.

Wu also discloses bispecific antibodies which have been engineered to combine the epitopic specificity of two of the disclosed murine mAbs. Applicants have directed the Examiner's attention to a published references (see **Exhibit A**) which make clear that bispecific antibodies necessarily contain two different epitope binding sites, each of which binds to a different epitope. Wu further discloses a bispecific antibody that binds simultaneously to two particular epitopes: epitope "Z" located exclusively in the ECL2 (which is recognized by 2D7) and epitope "Y" comprising amino acid residues in the Nt (which is recognized by 5C7), but the bispecific antibody of Wu does not bind to epitope "X".

The crux of applicants' argument is that whereas the

monospecific PA14 binds to the single epitope "X", comprising D2 in the Nt and R168 and Y176 in the ECL2 of CCR5, the bispecific antibody of Wu binds to two distinct epitopes, (1) epitope "Y", comprising P8 in the Nt, H88 and W94 in the ECL1, and possibly R274, L275, D276 in the ECL3, and (2) epitope "Z", located exclusively in the ECL2 and comprising Q170, K171 and E172. Applicants assert that epitope "X" is not the same as epitope "Y" or epitope "Z" because (a) "X" includes amino acid residue in both the Nt and ECL2 of CCR5, whereas "Y" includes amino acid residues in the Nt, ECL1 and ECL3, and "Z" is located exclusively in the ECL2; and (b) none of the amino acid residues in epitope "X" recognized by mAb PA14 corresponds to any amino acid residue in epitope "Z" identified by the 2D7 component of the bispecific antibody, or to any amino acid residue in epitope "Y" recognized by the 5C7 component of the bispecific antibody. The different epitopes recognized by mAb PA14 and the bispecific antibody of Wu, respectively, and the amino acid residues identified in these epitopes, are summarized in Table 1.

Applicants maintain that once the above distinction between the claimed invention and the disclosure of Wu is understood, it becomes clear that the claimed invention is neither anticipated by, nor obvious over, Wu.

In view of the foregoing remarks, applicants submit that the rejections set forth in the July 11, 2005 Final Office Action have been overcome. Accordingly, applicants request that the Examiner reconsider and withdraw the grounds of rejection contained therein, and earnestly solicit allowance of all claims now pending in the subject application.

Table 1. Amino acid residues identified in epitopes recognized by mAb PA14 and the bispecific antibody of Wu

Epitopes	Identified Amino Acid Residues	
	MAb PA14	Bispecific antibody of Wu
Epitope "X"[a]		
Amino terminus (Nt)	D2	Does not recognize epitope
1st extracellular loop (ECL1)	None	
2nd extracellular loop (ECL2)	R168 and Y176	
3rd extracellular loop (ECL3)	None	
Epitope "Y"[b]		
Amino terminus (Nt)	Does not recognize epitope	P8
1st extracellular loop (ECL1)		H88, W94
2nd extracellular loop (ECL2)		None
3rd extracellular loop (ECL3)		R274, L275, D276
Epitope "Z"[c]		
Amino terminus (Nt)	Does not recognize epitope	None
1st extracellular loop (ECL1)		None
2nd extracellular loop (ECL2)		Q170, K171, E172
3rd extracellular loop (ECL3)		None

[a] The residues in epitope "X" recognized by PA14 are identified in the specification of the subject application at page 33, lines 17-18.

[b] The residues in epitope "Y" recognized by the 5C7 component of the bispecific antibody of Wu are identified in Königs at page 1166, right col.

[c] The residues in epitope "Z" recognized by the 2D7 component of the bispecific antibody of Wu are identified in the specification of the subject application at page 33, lines 18-19. Lee also teaches that K171 and E172 are present in epitope "Z" (see page 9620, left col., first paragraph; page 9621, Figure 2B; and page 9625, paragraph spanning cols.)

Information Disclosure Statement

This Supplemental Information Disclosure Statement is submitted to supplement the Information Disclosure Statements filed February 24, 2005, January 7, 2005, August 12, 2004, July 22, 2004, June 3, 2004, September 3, 2003, June 3, 2003, June 14, 2001, and September 6, 2000 in connection with the subject application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit B**) and attached hereto as **Exhibits 1** and **2**:

1. Königs, C. et al. (2000) Monoclonal antibody screening of a phage-displayed random peptide library reveals mimotopes of chemokine receptor CCR5: implications for the tertiary structure of the receptor and for an N-terminal binding site for HIV-1 gp120. Eur. J. Immunol. 30(4): 1162-1171 (**Exhibit 1**); and

2. Lee, B. et al. (1999) Epitope mapping of CCR5 reveals multiple conformational states and distinct but overlapping structures involved in chemokine and coreceptor function. J. Biol. Chem. 274(14): 9617-9626 (**Exhibit 2**).

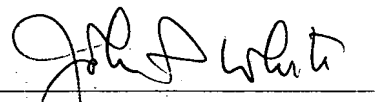
The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO-1449.

If a telephone interview would be of assistance in advancing

prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

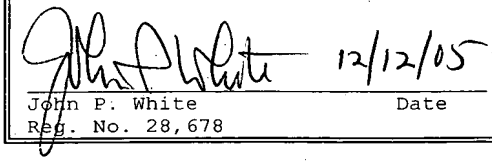
Pursuant to 37 C.F.R. 1.17(p), a fee of one hundred and eighty dollars ($180.00) is required for filing the Supplemental Information Disclosure Statement enclosed herewith. A fee of two hundred and twenty-five dollars ($225.00) is also required for a one-month extension of time for responding to the July 11, 2005 Final Office Action. Accordingly, a check in the total amount of FOUR HUNDRED AND FIVE DOLLARS ($405.00) is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



12/12/05

John P. White Date
Reg. No. 28,678